REMARKS

Status of the Claims

Claims 59-61, 63-79 and 94-96 have been withdrawn as being directed to a non-elected invention. Claims 39, 48-49, 56, 62, 80 and 82 are amended herein. These amendments are made solely to clarify the language of the claims and are not intended to modify the scope of the claims. Claims 81, 83-88, 90, and 92-93 are canceled herein and new claims 97-100 are added. Support for new claims 97 and 99 may be found on page 4, lines 30-33, and page 5, lines 10-11. Support for new claims 98 and 100 may be found on page 7, line 29, to page 8, line 20. Claims 39-58, 62, 80, 82, 89, 91 and 97-100 are pending.

Priority

A certified copy of United Kingdom application 9826247.0 filed November 30, 1998 is filed with this amendment and completes the requirements of 35 U.S.C. 119(b).

35 U.S.C. § 102

Claims 39, 43, 44, 55, 56 and 62 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Ji et al. (U.S. Patent No. 5,591,841). The applicants respectfully traverse this rejection.

Ji et al. discloses a method of purifying circular DNA using a "triplex capture complex." The capture complex consists of a single stranded oligonucleotide tagged with a biotin molecule. The single-stranded oligonucleotide binds to the double-stranded target of interest, forming a triple-helix structure. The target/biotin-labeled oligonucleotide is then captured on streptavidin-coated beads, as illustrated in Figure 1 of Ji et al.

Claim 39 as amended herein is directed to a method for separating nucleic acid molecules wherein a population of molecules is "tagged with a protein" and wherein the "protein

interacts directly with the matrix." Furthermore, the matrix must be one "which selectively binds proteins". Support for "which selectively binds proteins" is found on page 10 line 5.

The capture complex disclosed in Ji et al. does not use a tag that is a protein; it uses biotin (which is not a protein). Furthermore, the tag in this complex does not interact directly with the matrix; the biotin binds to streptavidin-coated beads. Additionally, the matrix is not one which "which selectively binds proteins"; the matrix is one which is streptavidin-coated, which binds biotin.

There is no teaching in Ji et al. that the tag should be a protein, nor is there any teaching that the tag should interact directly with a matrix. Further, there is no teaching of 'tagging' the nucleic acids to be separated. In Ji et al. the capture complex selectively binds to the nucleic acid of interest without the use of any 'tags.'

A claim is anticipated only if "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Because Ji et al. does not disclose a protein tag or that the tag must interact directly with the matrix or even that the nucleic acids to be separated are tagged, the Applicants assert that Ji et al. does not anticipate independent claim 39 nor claims 43, 44, 55 or 56, all of which depend from claim 39.

Claims 62 is directed to a method of separating linear from circular nucleic acid molecules by use of a tag, specifically by "introducing a tag to an end of a linear nucleic acid molecule". The tag must be a protein and the matrix must be one which "selectively binds proteins". Neither of these features are disclosed in Ji et al. As such, claim 62 is not anticipated by the disclosures of Ji et al.

Based on the forgoing discussion, the applicants respectfully request that the rejection of claims 39, 43, 44, 55, 56 and 62 be withdrawn.

35 U.S.C. § 103

Claims 45, 46, 80-86 and 93 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ji et al. in view of Seed (EP 580305).

Claims 83-86 and 93 are canceled herein. Applicants reserve the right to claim the subject matter of claims 83-86 and 93 in divisional or continuation applications. The applicants respectfully traverse the remaining rejections.

Claims 45 and 46 ultimately depend from claim 39 which, as discussed above, is directed to a method for separating nucleic acid molecules wherein a population of molecules is "tagged with a protein", wherein the "tag interacts directly with the matrix", and wherein the matrix is one "which selectively binds proteins".

Neither Ji or Seed teach or suggest that the tag must be a protein or that the tag must interact directly with the matrix as required by the present invention. Therefore the Examiner has failed to establish a *prima facie* case of obviousness for claims 45 and 46 in respect to Ji in view of Seed.

Claim 80 is directed to a method of separating nucleic acids into populations by use of a tag which can be immobilized on a matrix. Claim 80 requires that a population of molecules is "tagged with a protein", wherein the "tag interacts directly with the matrix", and wherein the matrix is one "which selectively binds proteins". Claim 80 further recites a particular arrangement of the porous matrix, an adsorbent pad and two liquid impermeable sheets, one of which has one or more holes. In particular claim 80 recites ". . . whereby the test sample is

applied to one of said holes and is caused to diffuse transversely through said porous material by absorption into said absorbent pad."

Ji does not disclose a matrix incorporated into a separation device. Seed discloses a separation device where a polypropylene grid supports a porous polyethylene disk which in turn supports a nitrocellulose membrane all of which is held in place with a Teflon sleeve. This assembly is mounted in a centrifuge tube with a tightly fitting cap. The sample is applied to the membrane and "The action of pushing the cap into place created positive pressure within the cartridge, thereby forcing the DNA-containing solution through the membrane." (column 10, lines 18-20).

The present invention differs from Seed in at least three important respects. First, the present invention teaches the use of two liquid impermeable membranes, one of which has one or more holes while Seed only discloses one membrane. Second, the membrane of Seed is permeable to liquid while the membranes of the present invention are not. Third, Seed relies on positive pressure to force the sample through the membrane into the porous matrix material while in the present invention the sample is applied to a hole in the membrane and diffuses through the porous matrix material by the absorption of an absorbent pad.

Therefore, Ji in view of Seed does not teach or suggest all of the limitations of independent claim 80 or claims 81-82 which depend from claim 80 and the Examiner has failed to establish a *prima facie* case of obviousness. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 47-54 were rejected under 35 U.S.C. § 103 as being unpatentable over Ji in view of Davis et al. (WO 90/12115). The applicants respectfully traverse this rejection.

Claims 47-54 depend from claim 39 and are directed to methods of separating nucleic acids that are the products of restriction enzyme digestion or the products of a PCR reaction.

Ji et al. does not teach separating nucleic acids from restriction enzyme digests or from PCR reactions. Davis et al. discloses that biotin may be used to label reaction products of PCR reactions for the purposes of separating out those populations (page 30 second paragraph).

However, claims 47-54 all depend from claim 39 and, as discussed above, claim 39 requires that the tag be a protein; biotin is not a protein. Furthermore, Ji in view of Davis does not teach or suggest all of the limitations of claims 47-54 and a *prima facie* case of obviousness has not been established. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 57 and 58 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ji in view of Dower et al. (US 5,427,908). The applicants respectfully traverse this rejection.

Claims 57 and 58 are directed to the method of claim 39 wherein the nucleic acid molecules are further subjected to in vitro packaging into bacteriophage particles. Because claims 57 and 58 depend from claim 39 they also include the limitations of the nucleic acids being "tagged with a protein" and the "tag interacts directly with the matrix."

Ji et al. does not teach the in vitro packaging of nucleic acids into bacteriophage particles. Dower et al. discloses the packaging of nucleic acids into bacteriophage for the purpose of separating out particular DNA sequences which code for a protein of interest. Neither Ji or Dower teach or suggest that nucleic acids must be "tagged with a protein" or that the "tag interact directly with the matrix" as taught by the present invention.

Further, Dower teaches that the nucleic acid is packaged in such a way that the protein for which it encodes is expressed on the surface of the bacteriophage thereby facilitating selection of phage that express a particular protein. The method of Dower is useful for the selection of particular DNA sequences from DNA libraries. One important distinction between Dower and the present invention is that in the present invention the separation of the nucleic acids occurs before bacteriophage packaging while in Dower the separation occurs after bacteriophage packaging. Also, Dower does not disclose the tagging of nucleic acids. In Dower, separation occurs based on binding to moieties that are on the surface of the phage not the packaged nucleic acids.

Based on the above discussion, the applicants believe that a *prima facie* case of obviousness has not been established and the applicants respectfully request the reconsideration and withdrawal of this rejection.

Claims 40-42 and 89-92 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ji in view of Wagner (US 6,120,992).

Claims 90 and 92 are canceled herein. Applicants reserve the right to claim the subject matter of claims 90 and 92 in divisional or continuation applications. The applicants respectfully traverse this rejection with regard to claims 40-42, 89 and 91.

Claims 40-42, 89 and 91 are directed to methods of separating nucleic acids by the use of nucleic acid binding proteins as tags. Ji does not teach the use of nucleic acid binding proteins in the separation of nucleic acids. Wagner discloses the use of DNA mismatch binding proteins to remove DNA sequences but does not disclose using the DNA mismatch binding proteins as tags for separating nucleic acids. In the method of Wagner, "immobilized mismatch binding proteins (MBPs)" are used for the separation of nucleic acids (column 6, lines 63-4 and

Fig. 17). Wagner does not 'tag' nucleic acids with MBPs but binds the MBPs to a matrix such as a bead and then uses the immobilized MBPs to separate the nucleic acids. Further, the invention of Wagner "depend on the creation of mismatches in the test DNA which are revealed by denaturing the test DNA and allowing it to reanneal." (column 7, lines 22-4) This is clearly not tagging a nucleic acid with a protein as required by the present invention.

Because neither Ji or Wagner disclose all of the limitations of claims 40-42, 89 or 91 the Examiner has failed to establish a *prima facie* case of obviousness and the applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 87-88 were rejected under 35 U.S.C. § 103 as being unpatentable over Ji in view of Cotton et al. (US 5,698,400). Claims 87-88 are canceled herein rendering this rejection moot. Applicants reserve the right to claim the subject matter of claims 87 and 88 in a divisional or continuation application.

CONCLUSION

Based on the foregoing amendments remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4290-4000. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4290-4000. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

Respectfully submitted,
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